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<p>(21) International Application Number: PCT/GB96/02041 (22) International Filing Date: 21 August 1996 (21.08.96) (30) Priority Data: 115564 11 October 1995 (11.10.95) IL (71) Applicant (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; 46 Jabotinsky Street, P.O. Box 4279, 91042 Jerusalem (IL). (71) Applicant (for SD only): WHALLEY, Kevin [GB/GB]; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): EYAL, Aharon, Meir [IL/IL]; Kibutz Ramat, 90900 Rachel (IL). VITNER, Asher [IL/IL]; 31/13 Stern Street, 96750 Jerusalem (IL). REUVENY, Tal [IL/IL]; 59/A Borochoy Street, 96781 Jerusalem (IL). (74) Agent: ABLEWHITE, Alan, James; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: A PROCESS FOR THE RECOVERY OF ASCORBIC ACID (57) Abstract The invention provides a process for the recovery of ascorbic acid from an aqueous feed solution containing the acid at a concentration of less than 0.7 mol/kg, including adsorbing a major portion of the ascorbic acid with a solid phase adsorbent resin selected from resins carrying a pyridine function and resins of similar or weaker basicity, separating the ascorbic acid-containing resin from residual aqueous solution, and subjecting the ascorbic acid-containing resin to a desorbing operation with a neutral solvent at a temperature of at least 20 °C higher than the temperature at which the adsorption is carried out, whereby there is obtained a solution of ascorbic acid in solvent in which the concentration of ascorbic acid is at least equal to its concentration in the aqueous feed solution.</p>		

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A PROCESS FOR THE RECOVERY OF ASCORBIC ACID

Background of the Invention

The present invention relates to a process for the production of ascorbic acid. More particularly, the present invention relates to the recovery of ascorbic acid from aqueous solutions containing the same in dilute concentrations.

As described, e.g., in Kirk-Othmer's Encyclopedia of Chemical Technology, Third Edition, ascorbic acid (L-ascorbic acid, L-xylo-ascorbic acid, L-threo-hex-2-enonic acid γ -lactone) is the name recognized by the IUPAC-IUB Commission on Biochemical Nomenclature for vitamin C. The name implies the vitamin's antiscorbutic properties, namely, the prevention and treatment of scurvy. L-ascorbic acid is widely distributed in plants and animals. The pure vitamin ($C_6H_8O_6$, mol. wt. 176.13) is a white crystalline substance derived from L-gulonic acid, a sugar acid, and synthesized both biologically and chemically from D-glucose.

Although natural and synthetic vitamin C are chemically and biologically identical, in recent years a limited amount of commercial isolation from vegetable sources, e.g., rose hips, persimmon, citrus fruit, etc., has been carried out to meet the preference of some persons for vitamin C from natural sources. L-ascorbic acid was the first vitamin to be produced in commercial quantities, and manufacture is based on the well-known Reichstein and Grussner synthesis, which involves the steps of hydrogenation of D-glucose to D-sorbitol; fermentation (oxidation) to L-sorbose; acetonation to bis-

isopropylidene-a-L-sorbofuranose; oxidation to bis-isopropylidene-2-oxo-L-gulonic acid, and hydrolysis, rearrangement and purification to L-ascorbic acid.

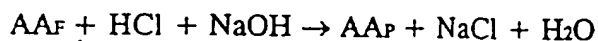
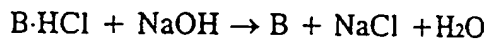
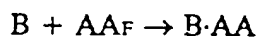
A direct fermentation of glucose to ascorbic acid would be very attractive, saving on operations and on expensive reagents, in addition to its being derived from a natural fermentation process, as opposed to a synthesis involving chemical steps. There are indications that such direct fermentation to ascorbic acid is feasible. Yet industrial production of ascorbic acid through direct fermentation seems impractical, in view of the low product concentration in the fermentation liquor, which normally is in the range of less than 0.7 mol/kg. Purifying the ascorbic acid by conventional methods would result in a purified product of concentrations similar to those in the fermentation liquor. Due to its high solubility in water, the cost of ascorbic acid crystallization by water evaporation would be prohibitive.

Several methods were proposed for combining purification of carboxylic acids with their concentration. In the case of citric acid, it is achieved by the addition of lime to crystallize calcium citrate, which has very low solubility in water. This salt is separated, washed and acidulated with sulfuric acid. Purified and concentrated citric acid is obtained. This method is not applicable for ascorbic acid, as its alkali and alkali earth salts are highly soluble.

A process was proposed in which carboxylic acids were extracted and then displaced from the extractant by a solution of concentrated mineral acids. Both liquid (long chain amines) and solid (resins carrying amine groups) anion exchangers could be considered for this purpose. The purity of the displaced carboxylic acid depends on the preference of the extractant to the mineral acid.

Such a process might be applicable for ascorbic acid separation and concentration, provided that the extractant is strong enough to reach high extraction yield, that it shows high preference to the displacing acid, and that the ascorbic acid is stable at the high acidity of the displacing solution.

The regeneration of the anion exchanger would require neutralization by a base. Using HCl as the displacing acid and distilling it off the extractant was proposed, but the high temperatures required and the extractant's decomposition at these conditions are prohibitive. If the anion exchanger is represented by B, the ascorbic acid in the fermentation liquor and in the pure form are AA_F and AA_P, respectively, the displacing acid is HCl, and the neutralizing base is NaOH, the equations of the process stages and of the overall reaction are as follows:



Reagents are consumed, and a by-product salt of no (or negative) value is produced.

Thus, despite the widely felt need for a more attractive process to meet the exceedingly high demand for ascorbic acid, to date no such process has been commercialized.

Summary of the Invention

With the above-described state of the art in mind, according to the present invention there is now provided a process for the recovery of ascorbic acid from an aqueous feed solution containing said acid at a concentration of less than 0.7 mol/kg, comprising adsorbing a major portion of said ascorbic acid with a solid phase adsorbent resin selected from resins carrying a pyridine function and resins of similar or weaker basicity; separating said ascorbic acid-containing resin from residual aqueous solution, and subjecting said ascorbic acid-containing resin to a desorbing operation with a neutral solvent at a temperature of at least 20°C higher than the temperature at which said adsorption is carried out, whereby there is obtained a solution of ascorbic acid in solvent in which the concentration of ascorbic acid is at least equal to its concentration in said aqueous feed solution.

The basicity of water-soluble bases is determined by the pH of their solutions. That of water-immiscible bases (fatty amines, basic resins) cannot be measured directly. Their apparent basicity is determined by various methods having one element in common: the water-immiscible base is contacted with an acid-containing aqueous solution. The degree of acid transfer from the aqueous solution into the water-immiscible base, or more particularly, the pH of the aqueous solution in equilibrium with the base, shows the apparent basicity. A theoretical treatment is given in several articles, including "Basicities of Weak Base Ion Exchange Resins," by Gustafson, *et al.*, Ind. Eng. Chem. Fundam., Vol. 9, p. 221 (1970). The authors of this article have studied the basicity of several resins by equilibrating them with aqueous amine-amine hydrochloride buffer solutions, followed by determination of the degree of neutralization α of

the resins as a function of the pH of the solution. As explained in the article, the pK of the resin is calculated from

$$\text{pK} = \text{pH} - \log \alpha/(1-\alpha)$$

Using this method for poly(2-methyl-5-vinylpyridine) cross-linked with 5, 7 and 10% divinylbenzene gave a pK of about 4.

Using other basicity measurement methods (for example, equilibration with HCl + NaCl solutions, as proposed by Nagasawa, *et al.*, Mem. Fac. Eng. Nagoya Univ., Vol. 10, p. 105 (1958) could result in different pK values for a particular resin. Yet, the relative basicities of resins can be determined by comparing their apparent basicity by one of the known methods. The resins suitable for the process of the present invention are those carrying a pyridine function and resins of similar, or weaker, basicity.

In preferred embodiments of the present invention, there is obtained a solution of ascorbic acid in solvent in which the concentration of ascorbic acid is higher than its concentration in said aqueous feed solution.

In the above process, at least 90% of said ascorbic acid is adsorbed by said solid phase adsorbent resin from said aqueous feed solution.

In preferred embodiments of the present invention, said solid phase resins are polyvinylpyridine polymers such as poly 2- and poly 4-vinylpyridine free base gel or macroreticular resins exhibiting a bead form. These resins are preferably at least about 2% cross-linked, and more preferably, at least about 8% cross-linked, with a suitable cross-linking agent, desirably divinylbenzene.

More preferred resins to date have been 2% to 25% cross-linked, bead form poly 2- and poly 4-vinylpyridine polymers. For example, preferred polymers in work to date have been poly 2- and poly 4-vinylpyridine resins available from Reilly Industries, Inc., Indianapolis, Indiana, in the REILLEX™ polymer series. These REILLEX™ polymers are 2% to 25% cross-linked, and exhibit good thermal stability and adsorptive and desorptive capacities and other preferred features as described herein.

The preferred resin beads can be of any suitable mesh size, for instance, from about 20 to about 60 mesh. Further, the resins can include a minor amount of functionalization of their pyridine groups, which minor amount can include, for example, functionalization to pyridine N-oxide or quaternary salt species. This functionalization has been incorporated to modify the relative basicity of the non-functionalized pyridine groups and thereby to modify their adsorptive and desorptive properties.

U.S. Patent 2,443,583 describes ascorbic acid separation through adsorption on an anion exchanger, followed by elution by a strong mineral acid, preferably H_2SO_4 . The excess of sulfuric acid is separated from the ascorbic acid through precipitation as gypsum. The anion exchanger is regenerated by a base, rinsed and acidified by a weak acid such as carbonic acid.

The process of said patent is complicated, consumes a strong acid and two bases, and forms two by-product salts of low or negative value. An objective of the process of the present invention is to avoid or reduce such chemical consumption and by-product formation.

In the process described in U.S. Patent 5,391,770, ascorbic acid is displaced from its alkali metal salt by a strong acid to its aqueous methanol solution, wherein the alkali salt of the mineral acid is only sparingly soluble. After separating the salt, the ascorbic acid-containing solution is passed through a cation exchange and anion exchange resins in order to remove the residual alkali metal salt of strong acid without adsorption of the ascorbic acid. The ascorbic acid is then isolated from the solution.

The process of U.S. Patent 5,391,770 is designed for separating ascorbic acid produced from 2-keto-L-gulonic acid and not ascorbic acid produced by fermentation, as in the present invention. The product concentration and the compositions and contents of the impurities accompanying it are also different. Therefore, U.S. Patent 5,391,770 does not teach purification and concentration of a fermentation product.

Kulprathipanja, in U.S. Patent 4,720,579, proposes a process for separating citric acid from a fermentation broth by contacting with a polymeric adsorbent selected from the group consisting of an insoluble crosslinked polystyrene polymer and a non-ionic hydrophobic insoluble polyacrylic ester polymer at adsorption conditions selected to selectively adsorb said citric acid. In another patent, U.S. Patent 4,851,573, Kulprathipanja proposes an adsorption process for separating citric acid from a fermentation broth by contacting with a water-insoluble, weakly basic, anionic exchange resin possessing tertiary amine or pyridine functional groups, at adsorption conditions selected to selectively adsorb said citric acid, desorbing said citric acid with a desorbent comprising water or a dilute inorganic acid at desorption conditions,

said adsorption conditions including pH lower than the first ionization constant of citric acid. This patent directs a strong preference for desorption by a dilute sulfonic acid, because in some cases water is not strong enough to recover the adsorbed citric acid. Desorption with a neutral solvent at a temperature of at least 20°C higher than the temperature at which the adsorption is carried out, is not claimed or exemplified. In fact, the second patent states, "Desorption conditions will include the same range of temperature and pressures as used for adsorption conditions."

U.S. Patent 4,323,702 claims a process for recovering a carboxylic acid from an aqueous solution by adsorption on a polymeric material having a pyridine skeletal structure and a cross-linked structure, followed by desorption through the use of a desorption agent selected from the group consisting of an aliphatic alcohol, an aliphatic ketone, and a carboxylic ester. The list of suitable carboxylic acids (column 3, lines 24-39) does not include ascorbic acid, which is not a carboxylic acid. The examples use propionic acid, benzoic acid, phthalic acid, malonic acid, tartaric acid, adipic acid, citric acid, methacrylic acid and acetic acid, all of which are carboxylic acids and not lactones.

Said patent claims that the resin is effective, even if the temperature of adsorption is high (column 3, lines 53-55), teaching away from elution at elevated temperatures. Elution at a temperature higher than the adsorption temperature was not shown in the examples of said patent. Furthermore, methanol and acetone were used as the desorbing agents in the examples. A nearly complete recovery of the acid from its aqueous solution was not shown or claimed, particularly not with a resin after being used and eluted.

The invention of PCT Application No. WO 93/00226 is directed to an extractive fermentation of lactic acid, whereby broth is continuously removed from the fermentor, separated from the cells and passed through a polymer phase-containing pyridine group. The main goal is to maintain the pH and the lactate concentration in the fermentor at levels that reduce the product inhibition in the fermentor. Elution (desorption) of the adsorbed acid is very briefly referred to: "The adsorbed lactic acid can be recovered using a suitable desorbing agent. Suitable desorbing agents will include, for example, polar organic solvents such as alcohols (e.g., methanol) as well as hot water" (page 10, lines 19-22).

Example 6 of said PCT application uses 5% solutions of NH_3 , H_2SO_4 or HCl for lactic acid desorption. Examples 2, 4 and 5 use methanol. No examples are given for the use of water for lactic acid desorption. No claim is made in said application to desorption at a temperature higher than that of the adsorption, or to obtaining the desorbed product at a temperature higher than that of the feed solution.

PCT Application WO 92/16490 relates to a process for recovering citric acid from a medium comprising it. In one preferred embodiment, the medium is contacted with a solid-phase, free base polymer having tertiary amine functions to adsorb citric acid, which is then desorbed by displacement with a strong acid, e.g., H_2SO_4 or HCl . In another preferred embodiment, the medium is contacted with a solid phase, free base polymer having pyridine functions at a temperature below about 40°C to adsorb citric acid, which is then desorbed with hot water at a temperature of at least about 75°C . No claim is made to achieving a product at a concentration higher than that of the feed.

In Example 1 of said application, a 10% citric acid solution was passed through a polyvinylpyridine polymer resin until the resin was saturated. The resin was then rinsed with CO₂ saturated water, and then was washed with water at 85°C. The citric acid concentration in the aqueous solution obtained (desorbate) was not given in the example.

In Example 3, a polyvinylpyridine resin was used in processes as described in Example 1, and the collected desorbed fluids were put back into the column after another saturation and rinse cycle, instead of water. The internal column temperature was brought to at least 85°C. According to WO 92/16490, "Using that technique, a concentration of up to about 10% citric acid is achieved in two cycles. Additional cycles can be performed to further increase citric acid concentration, but in Applicant's work thus far, due to decreasing usable capacity of the resin with each cycle, the best efficiency has been achieved after two cycles." Thus, Example 3 teaches that in order to desorb citric acid at concentrations similar to those of the feed, desorbate should be recycled to desorption. As a result, the desorption is not completed and the resin loses capacity in the next cycle.

Another aspect that was not referred to in PCT WO 92/16490 is that of the completion of citric acid recovery from the broth. Any acid left there forms a product loss. No data is given in the examples on how complete the recovery is. Yet, it is clear that desorption with citric acid-containing solution not only decreases the resin's capacity, but also decreases the efficiency of citric acid recovery from the medium.

In fact, the Applicant of PCT Application WO 92/16490, Reilly Industries, Inc., together with Advanced Separation Technologies, Inc., optimized and piloted their process. The pilot program results, as published in October, 1994, show a product concentration of 10% citric acid, compared to a feed concentration of 15%. The recovery was 95% or higher. Therefore, these results teach that operating the process at conditions allowing high recovery of the acid, results in a product that is more dilute than the feed.

Ascorbic acid is not a carboxylic acid, and one could not draw analogies from other acids as to its behaviour in adsorption on pyridine-based resins and in desorption. Yet, if such analogies could have been drawn, they would have indicated that product concentration on adsorption, followed by desorption at elevated temperature, is not attainable. An earlier publication by Reilly Industries, Inc. [Ernst and McQuigg, Paper No. 5AE, AICAE National Meeting (1992)] states: "The shape of the 25° equilibrium curve is quite favorable for adsorption...The 90° curve has the same shape, which is not favorable for stripping...The design, developed by Advanced Separations Technologies, Inc., indicates a product stream of 9% citric acid from a feed of 16% citric acid in broth."

The above statement is made for adsorption at 25°C and desorption at 90°C. The upper limit of the temperature range is determined in the case of citric acid by the various partial vapor pressures, by the overall pressure in the system and by the thermal stability of the resin. One should keep in mind that in the case of ascorbic acid, there is an additional limitation. Ascorbic acid tends to oxidize to dehydroascorbic acid, which decomposes rapidly to other

by-products. This oxidation could be enhanced by elevated temperatures and by the contact with the resin.

Thus, as seen from the above discussion, the state of the art does not teach whether binding to the pyridine based resin and desorption at elevated temperature is attainable without degradation of the ascorbic acid, and in fact, none of the above-mentioned publications teaches or suggests the process of the present invention.

As is well-known, a strong adsorbent is needed for high yield recovery from the feed solution. On the other hand, desorption is hindered by strong adsorbents, resulting in dilute desorbate solutions. The state of the art does not teach whether a pyridine based resin is strong enough to show high yields in adsorbing ascorbic acid from the dilute solutions and still weak enough to allow desorption at a concentration higher than its concentration in the feed.

While the invention will now be described in connection with certain preferred embodiments in the following example so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following example which includes preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood

description of formulation procedures as well as of the principles and conceptual aspects of the invention.

EXAMPLE 1

An aqueous solution comprising 7 g/l of ascorbic acid was contacted at 25°C countercurrently with a series of columns, comprising Rillex™ 425. The flow rate was 7 aqueous solution volumes per volume of resin, and the number of contacts was 7. More than 90% of the acid was adsorbed on the resin.

The resin was then washed at 80°C countercurrently with water. Here again, 7 stages were used. Practically all the adsorbed ascorbic acid was recovered, at a concentration of 10 g/l.

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A process for the recovery of ascorbic acid from an aqueous feed solution containing said acid at a concentration of less than 0.7 mol/kg, comprising:
 - adsorbing a major portion of said ascorbic acid with a solid phase adsorbent resin selected from resins carrying a pyridine function and resins of similar or weaker basicity;
 - separating said ascorbic acid-containing resin from residual aqueous solution, and
 - subjecting said ascorbic acid-containing resin to a desorbing operation with a neutral solvent at a temperature of at least 20°C higher than the temperature at which said adsorption is carried out,
 - whereby there is obtained a solution of ascorbic acid in solvent in which the concentration of ascorbic acid is at least equal to its concentration in said aqueous feed solution.
2. A process according to claim 1, comprising passing said aqueous feed solution through a column containing said resin.
3. A process according to claim 1, wherein said resin carries pyridine functions.
4. A process according to claim 1, wherein said neutral solvent is water.

5. A process according to claim 1, wherein said aqueous feed solution of ascorbic acid is obtained by fermentation.
6. A process according to claim 1, comprising adsorbing at least 90% of said ascorbic acid from said aqueous feed solution with said solid phase adsorbent resin.
7. A process according to claim 1, in which there is obtained a solution of ascorbic acid in solvent in which the concentration of ascorbic acid is higher than its concentration in said aqueous feed solution.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/02041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 403 351 (RHONE POULENC SANTE) 19 December 1990 cited in the application see the whole document ---	1-7
Y	US,A,2 443 583 (MOTTERN,H.M. ET AL.) 15 June 1948 cited in the application see the whole document ---	1-7
Y	EP,A,0 539 196 (HAYASHIBARA BIOCHEM LAB) 28 April 1993 see the whole document ---	1-7
Y	GB,A,760 575 (NATIONAL RESEARCH DEVELOPMENT) 7 November 1956 see the whole document ---	1-7
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

27 November 1996

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10 -12- 1996

Name and mailing address of the ISA

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Stellmach, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 16490 (REILLY IND INC) 1 October 1992 cited in the application see the whole document ---	1-7
Y	WO,A,93 06226 (TSAO GEORGE T ;LEE SEO JU (US); TSAI GOW JEN (US); SEO JIN HO (KR)) 1 April 1993 cited in the application see the whole document ---	1-7
Y	US,A,4 851 573 (KULPRATHIPANJA SANTI ET AL) 25 July 1989 cited in the application see the whole document ---	1-7
Y	EP,A,0 324 210 (UOP INC) 19 July 1989 cited in the application see the whole document ---	1-7
Y	US,A,5 068 418 (KULPRATHIPANJA SANTI ET AL) 26 November 1991 see the whole document ---	1-7
Y	US,A,5 068 419 (KULPRATHIPANJA SANTI ET AL) 26 November 1991 see the whole document ---	1-7
Y	KIRK-OTHMER: "Encyclopedia of Chemical Technology, 4th ed., Vol. 14," 1995, JOHN WILEY & SONS, NEW YORK XP002019618 * see pages 737-741 and 777-779 * -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0403351	19-12-90	FR-A- 2648136 AT-T- 126223 CA-A- 2018692 DE-D- 69021455 DE-T- 69021455 ES-T- 2075887 IE-B- 69381 JP-A- 3024068 SU-A- 1833383 US-A- 5391770	14-12-90 15-08-95 12-12-90 14-09-95 01-02-96 16-10-95 04-09-96 01-02-91 07-08-93 21-02-95
US-A-2443583	15-06-48	NONE	
EP-A-0539196	28-04-93	JP-A- 5117290 DE-D- 69201371 DE-T- 69201371 ES-T- 2071441 US-A- 5468850	14-05-93 23-03-95 13-07-95 16-06-95 21-11-95
GB-A-760575		NONE	
WO-A-9216490	01-10-92	AU-B- 670027 AU-A- 1583792 BR-A- 9205767 CA-A- 2106078 EP-A- 0576547 JP-T- 6506211	04-07-96 21-10-92 08-11-94 15-09-92 05-01-94 14-07-94
WO-A-9306226	01-04-93	EP-A- 0603321	29-06-94
US-A-4851573	25-07-89	CA-A- 1303061 US-A- 4720579 JP-A- 1191691 JP-C- 1727058 JP-B- 4012709 US-A- 4851574 US-A- 4924027 US-A- 5068419 CN-A,B 1034392	09-06-92 19-01-88 01-08-89 19-01-93 05-03-92 25-07-89 08-05-90 26-11-91 02-08-89

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/GB 96/02041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0324210	19-07-89	US-A- 4720579	19-01-88
US-A-5068418	26-11-91	NONE	
US-A-5068419	26-11-91	CA-A- 1303061	09-06-92
		US-A- 4720579	19-01-88
		JP-A- 1191691	01-08-89
		JP-C- 1727058	19-01-93
		JP-B- 4012709	05-03-92
		US-A- 4851573	25-07-89
		US-A- 4851574	25-07-89
		US-A- 4924027	08-05-90
		CN-A,B 1034392	02-08-89

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